

USARIEM TECHNICAL REPORT

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TOPICAL NITROGLYCERIN OINTMENT (2%) APPLIED TO FOREARM SKIN INCREASES SKIN BLOOD FLOW

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13. ABSTRACT (Maximum 200 words) It was hypothesized that topical nitroglycerin ointment (2%; nitropaste) applied to the forearm would increase forearm skin blood flow (SkBF). If so, nitropaste might be used to increase sensible heat flux from the forearm when it is applied under a forearm microclimate cooling system. Four men participated in four experiments each. The initial dose of nitropaste (NTG) was 7.5 mg. In each subsequent experiment (~one week from the previous), the dose was increased by an additional 7.5 mg until a final dose of 30 mg was achieved. In each experiment, the men were treated with nitropaste after sitting for a 15-min control period in slightly warm ambient conditions (Ta=30°C, Tdp=12°C). Prior to and after nitropaste was applied to the volar surface of the forearm (~36 cm ²), SkBF and heat flow were measured at the site by laser-Doppler velocimetry (LDV). Heart rate was measured by ECG every 2.5 min. and every minute following application. Laser-Doppler Imaging (LDI) was used to measure the difference in SkBF between placebo-treated application sites and nitropaste-treated application sites. There were no differences in cardiovascular responses among doses. The data reported are the mean of all four doses used during the dose response tests. The LDI Pilot Tests showed increased cutaneous vasodilation, but the LDV measurements taken in the dose response tests did not. This revealed the inability of LDV probes to provide consistent data as LDV measures a small area and LDI is capable of scanning the entire area. The area under the LDV would not receive NTG, but the adjacent area would. Topical nitroglycerin paste was shown to affect systemic vascular tone as seen by decreased diastolic blood pressure (DBP) and pulse pressure (PP) from baseline to treatment. In addition, DBP and PP were shown to significantly decrease further during recovery. In response to falling vascular pressures, heart rate increased from baseline to treatment and was also significantly higher during recovery. In contrast, systolic blood pressure was not significantly affected by treatment. These cardiovascular responses caused no unexpected side effects, although 75% of volunteers had headaches after the experiments.				
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TECHNICAL REPORT T01-03

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EXECUTIVE SUMMARY

It was hypothesized that topical nitroglycerin ointment (2%; nitropaste) applied to the forearm would increase forearm skin blood flow (SkBF). If so, nitropaste might be used to increase sensible heat flux from the forearm when it is applied under a forearm microclimate cooling system.

Four men participated in four experiments each. The initial dose of nitropaste (NTG) was 7.5 mg. In each subsequent experiment (~one week from the previous), the dose was increased by an additional 7.5 mg until a final dose of 30 mg was achieved. In each experiment, the men were treated with nitropaste after sitting for a 15-min control period in slightly warm ambient conditions ($T_a=30^{\circ}\text{C}$, $T_{dp}=12^{\circ}\text{C}$). Prior to and after nitropaste was applied to the volar surface of the forearm ($\sim 36\text{ cm}^2$), SkBF and heat flow were measured at the site by laser-Doppler velocimetry (LDV). Heart rate was measured by electrocardiography every 2.5 min. and every minute following application. Laser-Doppler Imaging (LDI) was used to measure changes in skin blood flux after application of 22.5 mg nitropaste in a single subject and was used in another experiment to measure the difference in SkBF between placebo-treated application sites and nitropaste-treated application sites.

There were no differences in cardiovascular responses among doses. Therefore, the data reported are the mean of all four doses used during the dose response tests. The LDI Pilot Tests showed increased cutaneous vasodilation, but the LDV measurements taken in the dose response tests did not. This revealed the inability of LDV probes to provide consistent data as LDV measures a small area and LDI is capable of scanning the entire area. The area under the LDV would not receive NTG, but the adjacent area would.

Topical nitroglycerin paste was shown to affect systemic vascular tone as seen by decreased diastolic blood pressure (DBP) and pulse pressure (PP) from baseline to treatment. In addition, DBP and PP were shown to significantly decrease further during recovery. In response to falling vascular pressures, heart rate increased from baseline to treatment and was also significantly higher during recovery. In contrast, systolic blood pressure was not significantly affected by treatment. These cardiovascular responses caused no unexpected side effects, although 75% of volunteers had headaches after the experiments.

INTRODUCTION

Scientific Background

The use of chemical protective garments (i.e., STEPO or MOPP) allows the soldier to perform tasks in life-threatening chemical/biological toxic environments where he/she would not ordinarily be able to survive (3). There are limitations to the use of these garments in hot environments because the soldier is unable to exchange the heat produced during exercise to the outside environment due to the impermeable nature of the garment. This heat, along with heat generated from the encapsulated self-contained rebreathing apparatus, causes temperatures to become high within the suit. The result is a rise in the individual's core and skin temperatures. Exercising in the heat while wearing a chemical protective garment significantly increases the rate of sweating, core temperature, and incidence the of heat illness, as opposed to individuals who are exercising in vapor permeable clothing (9).

In order to cool the skin within these suits, engineers have developed microclimate-cooling garments that work by circulating cool liquid/ice water through a series of flexible tubes within a form-fitting garment or blowing air across the skin. The use of these cooling garments enables soldiers to continue working/exercising within the encapsulated garments for longer durations. Rates of sweating, core temperature increases, and heat exhaustion have shown to be delayed through the use of microclimate cooling garments (8).

One well-known response to skin cooling in humans is a vasoconstrictive response of the skin blood vessels to increase resistance to heat loss (5). This leads to the blood being shunted away from the skin causing the cooling garment to be less effective for conductive and convective cooling. Thus, the individual's ability to dissipate heat through vasoconstricted skin blood vessels is less than if the skin blood vessels were to remain dilated. Theoretically, using a pharmaceutical agent to induce vasodilation of the cutaneous blood vessels would optimize heat dissipation when a liquid cooling garment is placed on the skin.

Nitroglycerin (NTG) in sublingual, intravenous, and topical application form has been shown to cause vessel dilation, although it is generally used in those individuals suffering from stenotic/atherosclerotic coronary vessels (1, 12). Intravenous infusion of nitroglycerin is used in the hospital setting to elicit the greatest vasodilator response and often results in profound hypotension. However, it has no practical application in the field. Although sublingual nitroglycerin treatment increases forearm temperature and skin blood

flow (15), it is our aim to minimize a systemic dilator response. It is our hypothesis that topical nitroglycerin (2%) will elicit a more localized effect on subcutaneous blood vessels while resulting in less incidence of hypotension and/or syncope, as opposed to the sublingual application.

It is our hypothesis that by dilating the skin blood vessels through the use of a pharmacological vasodilator, soldiers may be able to radiate more heat, show a slower rise in core body temperature, and thus perform more work. Most importantly, this approach might reduce incidence of heat illness.

Purpose

The purpose of this pilot experiment was to determine: (1) whether topically applied nitroglycerin 2% was effective in dilating skin blood vessels; (2) whether seated and resting subjects were able to maintain an adequate arterial blood pressure and avoid syncope and determine the safety of using increasing doses of NTG; (3) the minimal dose required to achieve the same maximal response (generate dose-response curves); and (4) whether or not skin temperature measurements provide useful information about how NTG affects heat flux through the skin.

Military Relevance

The use of chemical protective garments, in areas where enemies may have deployed chemical agents, is essential in protecting the health of our soldiers in the field. Heat stress poses a problem to the wearer (i.e., eliciting illness, limiting productivity by altering work/rest ratios, and/or causing cognitive impairment). Reducing heat stress by the use of an easy-to-apply topical vasodilator agent, used together with microclimate cooling technology, may enable soldiers to perform more effectively and for a longer duration in chemical protective clothing.

METHODS

Test Subjects

Four men were recruited as test subjects for the dose-response studies. The mean \pm standard deviation (S.D.) age, height, weight, and body surface area for the subjects was 37.0 ± 6.3 yrs., 168.9 ± 3.3 cm, 75.2 ± 15.0 kg, and 1.9 ± 0.2 m², respectively. One of

the test subjects (NPP-04) also volunteered for Pilot Test 1 and another (NPP-02) volunteered for Pilot Test 2.

Experimental Design

Environmental Conditions

The ambient dry bulb temperature was 30°C, and the ambient dew-point temperature was 12°C, during all testing.

Dose/Response Tests

Each volunteer participated in four experiments on each of 4 days, with at least a week between experiments. In the first experiment, a 7.5 mg dose of nitropaste was applied to the forearm skin. An additional 7.5 mg dose of nitropaste was applied to the forearm for each subsequent experiment, which resulted in nitropaste doses of 15.0, 22.5, and 30.0 mg. Skin blood flow (SkBF), heat flow, skin temperature, heart rate, and blood pressure responses were determined for each experiment.

Pilot Test 1

Laser-Doppler Imaging (Moor Instruments) was used so that the skin blood flow on a whole area of skin exposed to nitropaste (22.5 mg) could be seen in one subject (NPP-04). This test was designed to be used to visually indicate vasodilation in the area under and around the application site.

Pilot Test 2

Laser-Doppler Imaging software (Moor Instruments) was used to measure skin blood flow at two quarter-sized sites on one forearm on which a placebo had been applied to the ventral surface of the forearm. These sites were compared to two nitropaste-treated sites of the same area (7.5 mg/site) on the contralateral forearm. The treatment applied to both sites of the left arm and placebo on both sites of the right forearm.

Nitropaste Application

Topical nitroglycerin (2%, Fougera & Co. Melville, NY) was applied over a 9 x 4 cm (36 cm²) area for each dosage (7.5, 15.0, 22.5, and 30.0 mg). The paste was measured by the use of the supplied dosing papers (0.5" \approx 7.5 mg, 1.0" \approx 15.0 mg, 1.5" \approx 22.5 mg, 2.0" \approx 30.0 mg) provided by the manufacturer. Prior to measurement, a pea-sized amount from the tip of the tube was discarded to eliminate the potential for administering an oxidized sample.

Test Procedures

Dose Response Tests

The test subjects fasted overnight and refrained from drinking alcohol 36 h prior to the experiment. Water ingestion was permitted until the experiment started. The time of the experiment was approximately the same time of day for each test subject for all experiments (starting between 0700-0800 h or between 1200-1300 h) to control for circadian differences in skin blood flow and thermoregulation within subjects (14).

The test subjects entered the environmental test chamber dressed in shorts, singlet, shoes, socks and underwear. Male subjects often chose not to wear the singlet, but the clothing chosen was the same for all experiments. Electrocardiographic electrodes and leads were attached to the torso and monitored for rate and rhythm in Lead II. The volunteer was weighed and then sat on the chair of the modified cycle ergometer. Thermistors and heat flow disks were attached to the skin at eight sites: left hand; left chest, at the axillary fold; left medial shoulder; right side of back, \sim 8.0 cm below the acromion process; lateral region of right calf; medial region of the thigh; center of forehead, just above brow; and left forearm. Laser Doppler velocimetry (Vasamedics, St. Paul, MN) was used to measure SkBF (11) at two sites on the forearm. One site was located within the forearm application site. The other was attached to the forearm skin proximal to the nitropaste application site. An automatic blood pressure monitor (Accutorr 1A, Datascope, Inc., Paramus, NJ) was used to determine systolic and diastolic blood pressure and to determine mean arterial pressure. The experiment was designed so that if mean arterial pressure were to drop to 60 Torr in any individual, the paste would be removed promptly and actions to correct symptomatic hypotension would be initiated.

After all instruments were attached to the subject, a 15-min control period was started. Skin temperatures, forearm SkBF, and heat flow were measured every 0.5 min, and blood pressure and heart rate were measured every 2.5 min. An investigator applied

nitropaste within the 36 cm² area on the ventral surface of the forearm by spreading the ointment around one LDV and one heat flow disk. Blood pressure and heart rate measurements were made each minute after nitropaste application. After 20 min, nitropaste was gently scraped from the skin by an investigator using a small stainless steel spatula. All measurements were made for another 15 min. Instruments were removed, and the subject was weighed. The forearm skin site where nitropaste had been applied was then washed using mild dish detergent and water.

Pilot Study 1

Subject (NPP04) was prepared for testing as mentioned in the dose response tests; however, only ECG and blood pressure were measured for safety. Nitroglycerin (22.5 mg) was applied to the ventral surface of the forearm following a brief (~10 min) control period. Skin blood flow was visually monitored by LDI with repeat scans occurring ~ every 5 min. The paste was taken off ~15 min later, and the subject remained still for another 20 min for repeat scans.

Pilot Study 2

The subject (NPP-02) was prepared for testing as mentioned in the dose response tests, however, only ECG and blood pressure were measured for safety. Four quarter-sized regions, two on each forearm, were made on the ventral surface. Following a 10-minute control period, 7.5mg. NTG was applied to each site on the left arm, and a placebo was applied on each site on the right arm. The subject was blind to content of all sites. The NTG paste and placebo were both left on for ~ 15 minutes with scans occurring every 5 minutes, followed by removal and continued scans at the same interval for ~15 minutes. The sites were denoted as left proximal (LP), left distal (LD), right proximal (RP), and right distal (RD).

Calculations

Mean skin temperature was determined by the following:

$$T_{sk} = (0.07 \times T_{head}) + (0.175 \times T_{chest}) + (0.175 \times T_{back}) + (0.07 \times T_{upper arm}) + (0.07 \times T_{forearm}) + (0.05 \times T_{hand}) + (0.19 \times T_{thigh}) + (0.20 \times T_{calf})$$

Mean heat flow was determined by the following:

$$HF = (0.07 \times HF_{\text{head}}) + (0.175 \times HF_{\text{chest}}) + (0.175 \times HF_{\text{back}}) + (0.07 \times HF_{\text{upper arm}}) + (0.07 \times HF_{\text{forearm}}) + (0.05 \times HF_{\text{hand}}) + (0.19 \times HF_{\text{thigh}}) + (0.20 \times HF_{\text{calf}})$$

Mean arterial pressure was determined by the following:

$$MAP = (SBP-DBP)/3 + DBP$$

Pulse pressure was determined by the following:

$$PP = SBP-DBP$$

Data Analyses

Two-way analyses of variance (ANOVA) with repeated measures were used to determine differences in the physiological parameters (Nitropaste dose x Time). When no differences among doses were found, the data were combined to determine the percentage of change in each physiological parameter during the 20-min treatment and 15-min recovery periods.

RESULTS

Thermal Responses

Mean skin temperature decreased from baseline to treatment by $0.1 \pm 0.3\%$ and by $0.3 \pm 0.5\%$, during recovery (Figure 1), although not significantly. Mean heat flow decreased significantly from baseline to treatment by $7.6 \pm 4.2\%$ and by $9.4 \pm 4.1\%$ during recovery ($P < 0.05$) (Figure 2).

Figure 1: Change in Mean Skin Temperature

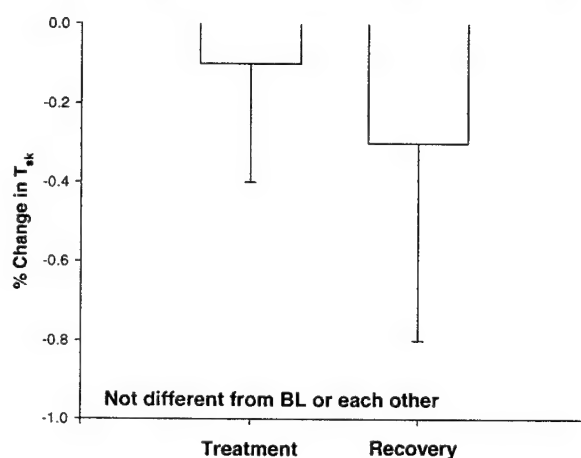
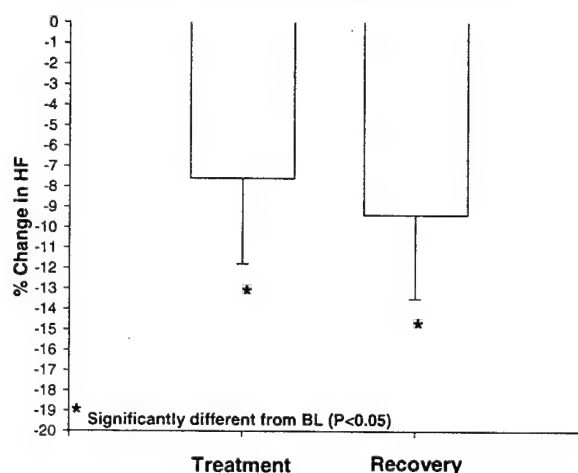


Figure 2: Change in Mean Heat Flow



Cardiovascular Responses

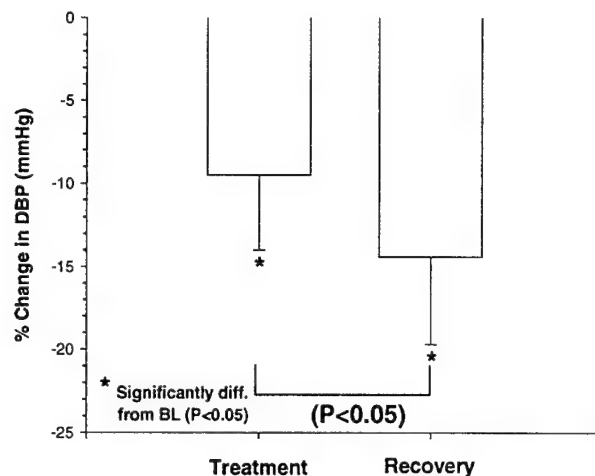
All subjects participating in the dose/response tests, and Pilot 1 and 2 tests were able to maintain arterial blood pressure >60 Torr throughout all dosages. Although there were no incidences of hypotension and/or syncope, side effects included mild headache in 75% of subjects (common with Nitrate vasodilators) and one case of urticaria within the application site at one dose only.

Dose/Response Tests

There were no statistically significant differences in cardiovascular responses between any of the doses; therefore, data are reported as the mean of four doses.

Systemic vascular relaxation was evident by the evaluation of diastolic pressure values. Diastolic pressure decreased from baseline by 9.5 ± 4.5 % during treatment and by 14.4 ± 5.3 % during recovery. A significant difference was seen between all three phases ($p < 0.05$) (Figure 3).

Figure 3: Change in Diastolic Blood Pressure



Mean arterial pressure decreased from baseline by 4.2 ± 4.5 % ($P < 0.05$) during treatment and by 0.6 ± 2.1 % during recovery (Figure 4). The treatment/recovery interaction was significant ($P < 0.05$). Systolic blood pressure was not affected by nitroglycerin application (Figure 5).

Figure 4: Change in Mean Arterial Pressure

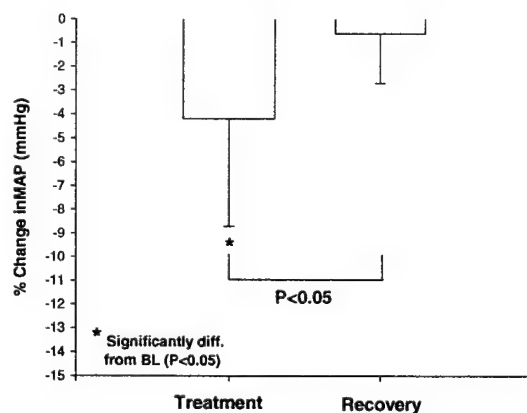
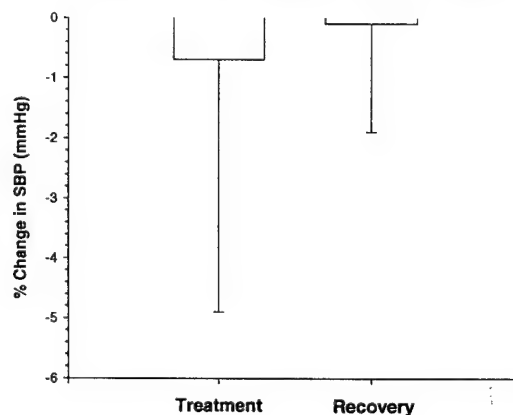
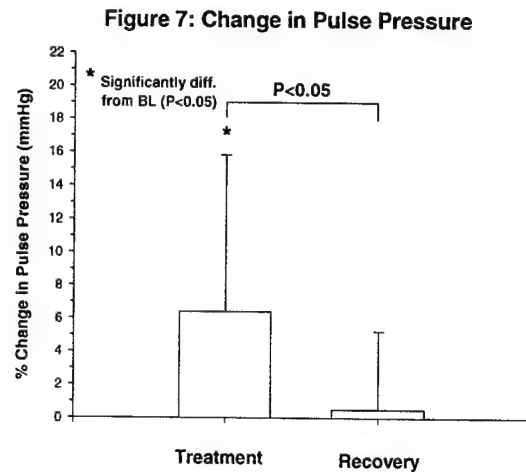
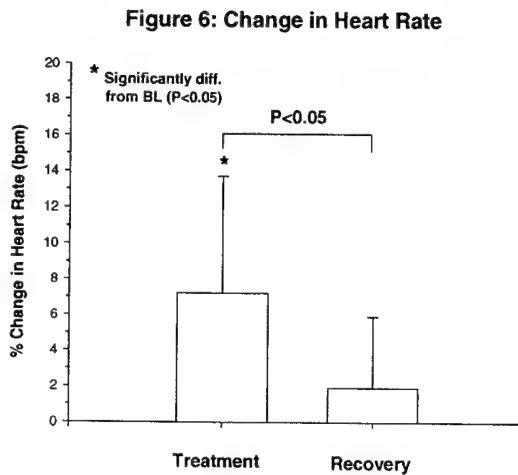


Figure 5: Change in Systolic Blood Pressure



Heart rate increased from baseline by $7.2 \pm 6.5\%$ ($P < 0.05$) during treatment and by $1.9 \pm 4.0\%$ (NS) during recovery, with significant differences noted between treatment and recovery phases ($p < 0.05$) (Figure 6). Pulse pressure also increased from baseline with nitroglycerin application by $6.4 \pm 9.4\%$ ($P < 0.05$) during treatment and by $0.5 \pm 4.7\%$ (NS), with significant differences noted between treatment and recovery phases ($P < 0.05$) (Figure 7).



These data show that topically applied nitropaste is associated with systemic vasodilation (Table 1). After nitropaste application SkBF, as measured by LDV, increased by $3.5 (\pm 3.3)$ ml/100ml/min from control ($P < 0.05$) for the 22.5 mg challenge only. Although statistically significant, LDV measurements showed variable responses between subjects, as well as during each subject's test for all other doses. This leads us to conclude that no increase with the exception of a small increase in NPP04, occurred outside the application site, and measurements taken within the application site may be confounded by pressure applied by the probes and/or inability of the NTG to circulate underneath the probes. The color of the skin within the treatment site was noted to be a pink color following removal of nitropaste, compared to the color noted prior to application indicating, subjectively, that SkBF had increased.

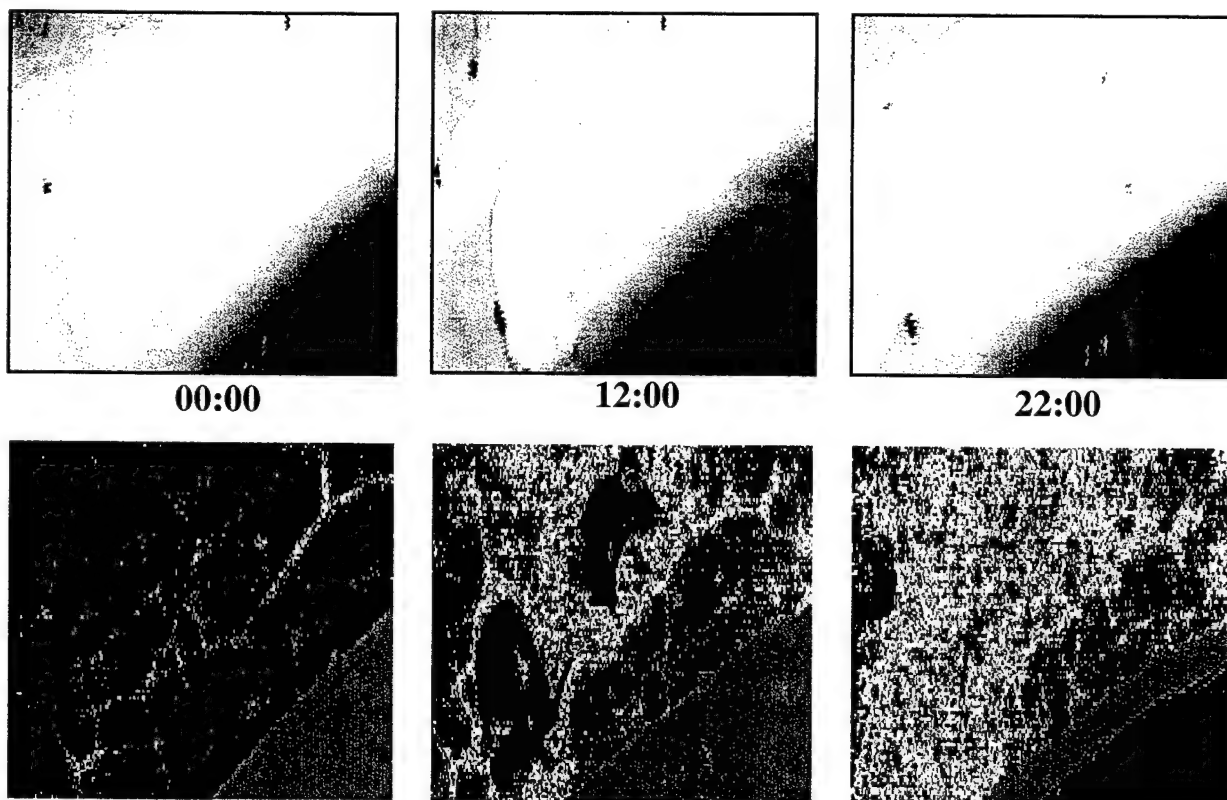
Table 1: Cardiovascular Variables for Dose Response Testing
Percent Change From Baseline

	SBP	DBP	MAP	HR	PP	Tsk	HF
Tx.	$-0.7 \pm 4.2\%$	$-9.5 \pm 4.5\%$	$-4.2 \pm 4.5\%$	$7.2 \pm 6.5\%$	$6.4 \pm 9.4\%$	$0.1 \pm 0.3\%$	$7.6 \pm 4.2\%$
Rec.	$-0.1 \pm 1.8\%$	$-14.4 \pm 5.3\%$	$-0.6 \pm 2.1\%$	$1.9 \pm 4.0\%$	$10.5 \pm 4.7\%$	$0.3 \pm 0.5\%$	$9.4 \pm 4.1\%$
Sig.	NS	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	NS	$P < 0.05$

Pilot Trial 1

As previously mentioned, Pilot Trial 1 was used as a visual confirmation that topical nitroglycerin is capable of dilating skin blood vessels. Although the data could not be quantified by skin blood flow measurements, within 6 min of nitropaste application, a significant dilation was noticed first around the treatment site, and by 15 min, a widespread dilation was identified following the removal of the NTG paste (Figure 8). Top three boxes are DC photos and bottom three boxes are LDI scan images. Notice, at 12 min, although the LDI is incapable of scanning through the paste due to its opaque properties, dilation is still occurring adjacent to the paste. Again, as in all the experiments conducted, mean arterial blood pressure was maintained well above 60 Torr.

Figure 8: Reference Point Photographs vs. LDI Scans for Pilot Test 1



Pilot Test 1: Pilot Test 1 was used as visual confirmation that Nitropaste is capable of dilating skin blood vessels. Nitropaste was applied at 5.0 minutes and removed at 22.0 minutes. Vasodilation is seen as early as 12.0 minutes (lighter colors yellow-red), and vasodilation continues well after NTG removal. Top three pictures are photographs of skin surface and bottom three pictures are LDI images. Note that the opaque properties of NTG paste made it impossible to see the magnitude of vasodilation until removal.

Pilot Trial 2

Laser Doppler Imaging software was used in Pilot Trial 2 to quantify the degree of vasodilation seen in Pilot Trial 1 (Table 2). Average skin blood flow for Pilot Trial 2 increased 157%, 112%, and 129% from baseline for 22:00, 29:00, and 36:00 min measurements, respectively, on the NTG-treated arm, opposed to 21%, 8%, and 1% for 22:00, 29:00, and 36:00 min measurements, respectively, on the placebo-treated arm (Figures 9 & 10). Cutaneous vasodilatation was noted (reddening of the skin) upon visual examination of the skin sites on which nitropaste was applied. Note that treatment sites left proximal (LP) and left distal (LD) showed increased blood flow to the cutaneous vessels (Figure 9). Figure 10 shows the images made using LDI.

Table 2: Cardiovascular Responses for Pilot Test 2

Time	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)	LDI (mV)	LDI (mV)	LDI (mV)	LDI (mV)
					L-Distal	L-Prox.	R-Distal	R-Prox.
0.00	111	69	83	72	807.20	731.10	606.20	541.60
10.00	113	66	82	80	768.20	809.10	969.10	716.90
16.50	112	70	84	74	1100.70	1074.00	961.90	680.50
22.67	113	71	85	78	2113.10	1833.80	840.70	551.00
29.08	117	68	84	73	2001.20	1264.00	842.50	402.70
36.03	113	69	84	86	1844.40	1677.10	662.10	501.00

Figure 9: Effect of 15 mg Topical NTG on Skin Blood Flow at 4 Sites Using LDI

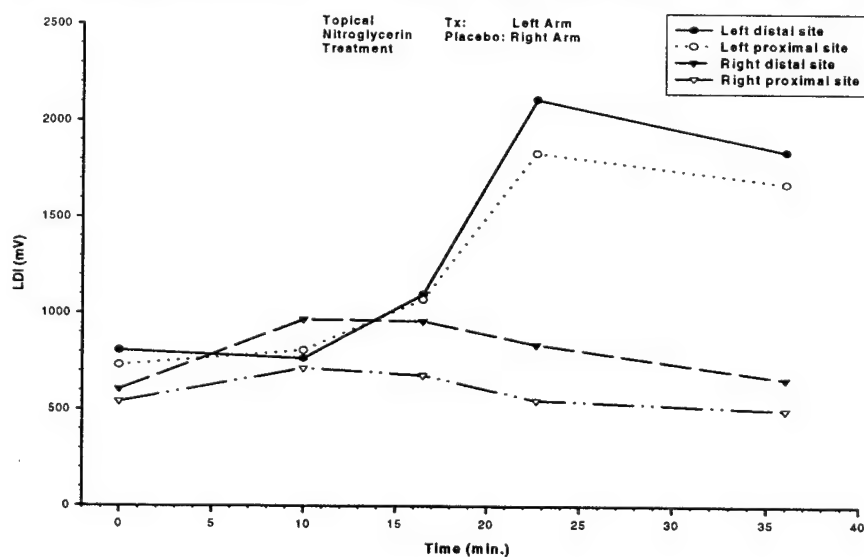
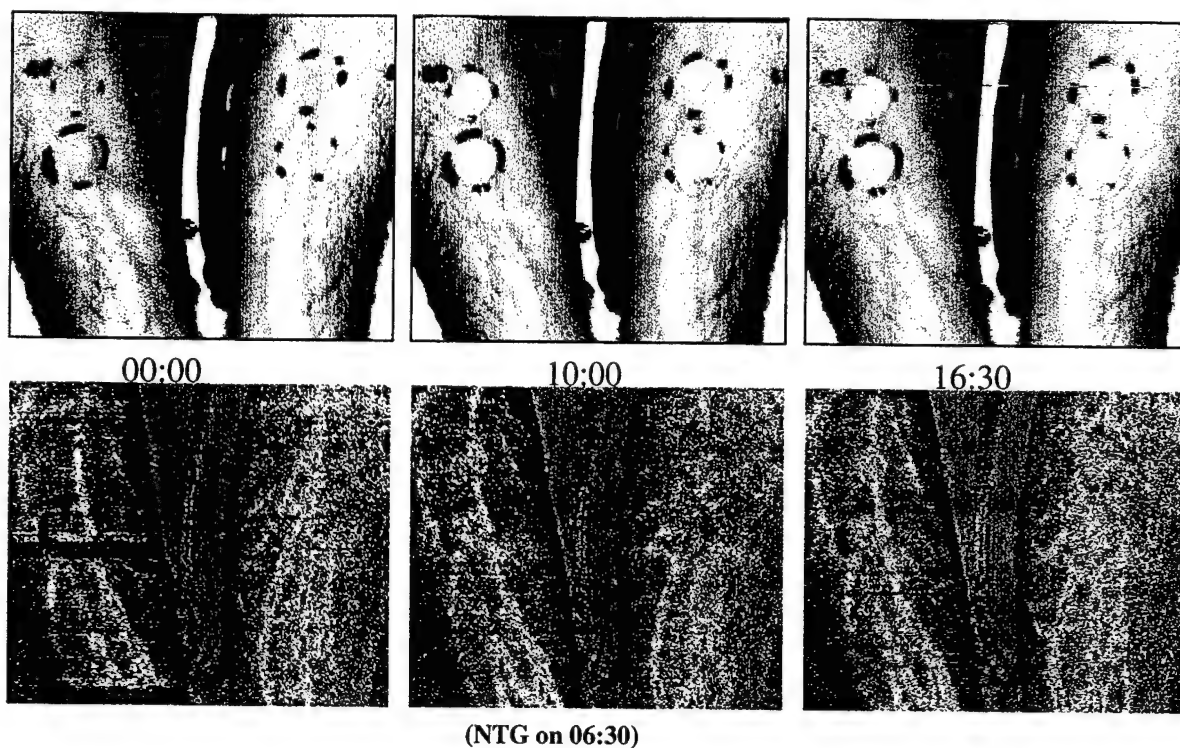
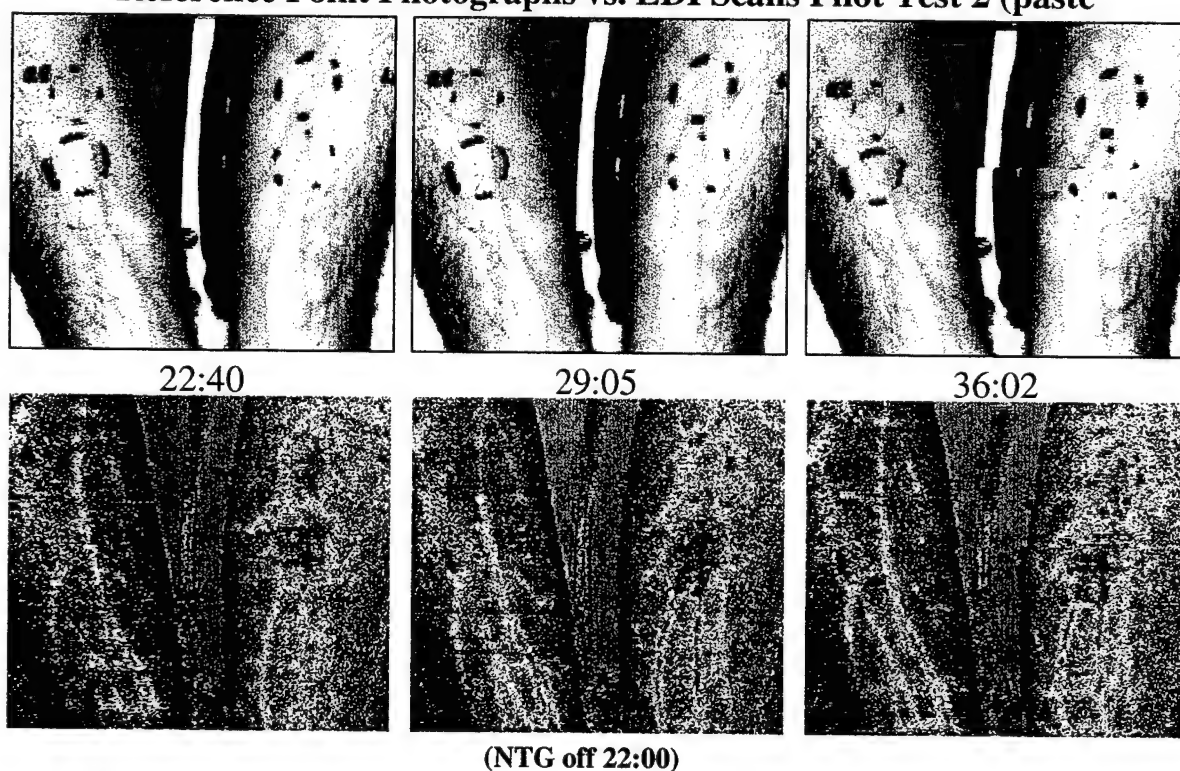


Figure 10: Reference Point Photographs vs. LDI Scans Pilot Test 2 (baseline/paste on)



Reference Point Photographs vs. LDI Scans Pilot Test 2 (paste



Pilot Test 2: Blood flow as determined by Laser Doppler Imaging software (Moor Medical) increased 157% in left arm (769 mV to 1973 mV mean) and 21% in right arm (573 mV to 696mV mean) 15 min following removal of paste, indicating localized vasodilation with topical application. Top three boxes are photographs of skin surface and bottom three boxes are LDI images.

Subjective Responses

Following all experiments, subjects were questioned to uncover any symptoms they had experienced during testing or were presently experiencing. Approximately 75% of all experiments resulted in the development of mild headaches, commonly seen in coronary patients who routinely use topical nitroglycerin (12, 13). As previously mentioned, there were no instances of syncope or near syncope during any of the trials.

DISCUSSION

Nitropaste application caused significant cutaneous vasodilation when measured by LDI (Table 2). This observation is limited to the Pilot Studies (Figures 8-10), but we are confident that vasodilation occurred in all cases based on a distinctive change in forearm skin color at the application site. We have also shown that in Pilot Trials 1 & 2, LDI can detect changes in skin vessel dilation, and the accompanying software has the capability to quantify such changes for statistical analysis. Single-point laser Doppler velocimetry probes were not adequate for evaluating the effect of nitropaste on skin blood flow, mainly because absorbed NTG apparently did not diffuse under the probe due to the pressure exerted on the surface of the skin by the attached probe. In addition, in several experiments, the laser-Doppler probe affixed to the application site malfunctioned intermittently thereby increasing the variability of skin blood flow measurements.

The seated volunteers were able to adequately maintain mean arterial blood pressure (Figure 4). Topical nitropaste significantly reduced both mean arterial blood pressure and diastolic blood pressure values only (Figures 3-4). The dose response evaluations indicated that topically applied nitropaste, as expected, dilates arterial vessels (increases in pulse pressure despite the failure of systolic blood pressure to increase), and cardiac output is presumably maintained primarily by increases in heart rate in trained human subjects. Thus, it is suspected that maintenance of mean arterial blood pressure is not compensated by increases in systolic blood pressure, but rather cardiac frequency, in our study population.

The maximal dose to achieve a decreased diastolic pressure may be 7.5 mg. However, our study population is probably too small to answer that question. The smallest dose (7.5 mg) was almost enough paste to be spread over the entire surface area of the application site. When the higher doses were used, the paste was applied more thickly, so that the area of nitropaste contact with the skin did not change very much. If the contact area of nitropaste with the skin surface was the limiting factor for absorption, then one would expect that there would not be a statistically significant change in diastolic pressure with increasing dose of nitropaste.

Mean skin temperature was shown to have decreased during treatment and even further during recovery. In accordance, mean heat flow also decreased from baseline to treatment and decreased even further during recovery.

Limitations of the Study

The primary purpose of this study was to determine the safety of administering nitropaste to resting, seated humans. The major limitation of the study was that a placebo paste was not used as a control. Consequently, the declining diastolic blood pressure may have simply been the result of the subject's seated posture and the possibility for relaxation that occurred over the time of the study. Yet, it is unlikely that only diastolic blood pressure and not systolic blood pressure would be affected by time of seated posture and relaxation. Increased heart rate is evidence that the diastolic pressure response is not due to seated posture alone. In addition, to be confident that there is not a dose response to nitropaste, a larger study population may be needed.

CONCLUSIONS

Although our subject population was small ($n=4$), we have shown that there were no significant differences in responses with successive doses of topical nitroglycerin applied to a consistent area of the forearm. This may suggest that if the results of this study were to be duplicated on a larger population, the cardiovascular responses shown with topical application would be limited to the treated skin surface area.

In addition, there is evidence that healthy trained males increase their heart rate as a response to compensate for dilated arterial vessels. Further evaluation is required to determine whether or not stroke volume is also increased when subjects are faced with a vasodilatory challenge.

RECOMMENDATIONS

We have shown that seated, resting subjects are able to maintain adequate arterial blood pressure. The next step is to investigate whether or not upright posture or exercise in hot, cold, and thermoneutral environments will modify the physiological responses to nitropaste before the safety and effectiveness of using nitropaste as a vasodilatory aid can be determined. Although nitropaste does elicit cutaneous vasodilation, it must be demonstrated that application of nitropaste improves exercise tolerance from measurements of core temperature, skin temperature, heart rate, and arterial blood pressure during exercise. Finally, a future study might be conducted to determine whether the lowest dose of nitropaste can be spread over a larger surface area to cause greater cutaneous vasodilation.

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